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Stereo- and regiospecific formation of a highly functionalized bridgehead tricyclic sultam

Daniel D. Long,[a] Russell Dahl,[b] Catherine Jolivet,[b] Will J. Marshall[c] and Andreas P. Termin[b,*]

[a]*Advanced Medicine Inc., 901 Gateway Blvd., So. San Francisco, CA 94131, USA*
[b]*Bristol-Myers Squibb Pharma Research Laboratories, Suite 400, 4570 Executive Drive, San Diego, CA 92121, USA*
[c]*E.I. DuPont de Nemours & Co, E228/326, PO Box, Wilmington, DE 19880-0228, USA*

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Abstract—Tethering of a nitrone moiety to an olefin containing endocyclic sultam results in high yielding spontaneous intramolecular nitrone–olefin cycloaddition. The reaction proceeds with complete regio- and stereospecific control to establish three new chiral centers in the tricyclic products which incorporate an unusual bridgehead sultam motif. A transition state model for the remarkable regio- and stereochemistry is supported by NMR analysis and X-ray crystal diffraction. Three sites of chemical diversity are highlighted which make the tricyclic template an attractive combinatorial scaffold. © 2002 Published by Elsevier Science Ltd.

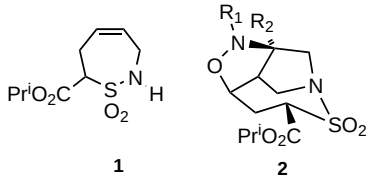
The sulfonamide moiety present in the 'sulpha' antibiotics of the 1930s was central to the birth of synthetic drug therapy.[1] Since that time an enormous number of sulfonamides including cyclic variants (sultams) have been synthesized and shown to have important applications particularly in veterinary therapeutics[2] and chemical methodology (e.g. the Oppolzer sultam chiral auxiliary).[3] In recent years, the relative ease of derivatization and ubiquitous biological activity of the sulfonamide motif has made it a common constituent of combinatorial small molecule libraries. A report in 1999 by Paquette detailed the first example of a *small bridgehead bicyclic sultam* which was shown to be stable.[4]

We recently reported the synthesis and combinatorial derivatization of the novel endocyclic sultam **1** as the enantiomeric mixture.[5] Expanding upon our program to develop novel, functionalized templates we sought to derivatize the olefin moiety of **1** in a stereo- and regioselective manner. This report describes the utilization of a tethered intramolecular nitrone cycloaddition to the olefin, which provides entry to the novel class of bridgehead tricyclic sultam **2** (Fig. 1).

The intramolecular 1,3-dipolar nitrone–olefin cycloaddition reaction was pioneered by LeBel,[6] and has received great attention.[7] Of particular interest has been the cycloaddition of 5-hexenyl-1-nitrone systems **3**, which typically yield a *cis*-fused 3-oxa-2-azabicyclo[3.3.0] octane system **4** with high regio- and stereoselectivity (Scheme 1).

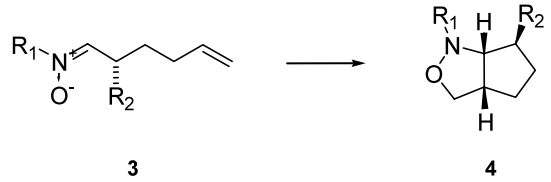
We envisaged tethering a reactive nitrone moiety to the sulfonamide NH of template **1** to obtain a heteroatom substituted 5-hexenyl-1-nitrone motif **5** partly integrated into the ring system (Fig. 2).

We were intrigued as to whether the intramolecular cycloaddition would occur with the expected high level of regio- and stereocontrol demanded by the restrained transition state, and whether the remote stereocenter of



1 2

Figure 1.



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Scheme 1.

* Corresponding author. E-mail: atermin@combichem.com

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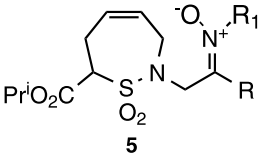


Figure 2.

the enantiomeric substrate would exert an asymmetric induction.

In a previous report, we described the high-yielding and selective *N*-alkylation of the sulfonamide **1** with a set of simple alkyl bromides.[5] Treatment of the template **1** with 1 equiv. of α-halo ketone in DMF in the presence of potassium carbonate similarly yielded the *N*-substituted ketones **6a–c** in reasonable yield (60–91%; no *C*-alkylation was observed) (Scheme 2). Initial investigation into formation of a nitrone motif such as **5** involved reaction of the ethyl ketone **6a** with methyl hydroxylamine in benzene at 90°C. After 12 h a single peak was observed by LC mass spectrometry corresponding to the nitrone product. However, following HPLC purification, NMR analysis revealed that the single mass peak consisted of a major product **7a** which appeared to be a result of intramolecular nitrone–olefin cycloaddition (characteristic olefin signals were absent), and a minor amount of the uncyclized nitrone–olefin. The products share the same molecular mass and were unfortunately inseparable.

In an effort to more clearly follow the cycloaddition reaction the synthesis of the nitrone–olefin precursor was attempted using polar conditions.[8] Thus, reaction of the ethyl ketone **6a** with 2 equiv. of methyl hydroxylamine in ethanol in the presence of 4 equiv. of sodium acetate was performed at room temperature. After a period of 24 h LC–MS revealed complete conversion of the starting ketone to a single product. Purification and NMR analysis confirmed material **7a** was in fact formed in 94% yield. Utilizing the same conditions, the methyl ketone **6b** underwent analogous conversion over 4 h to give **7b** in 87% yield while the bulkier phenyl ketone **6c** required 4 equiv. of methyl hydroxylamine and 8 equiv. of sodium acetate in ethanol (80°C over 24 h) to afford the cyclized product **7c** (70%).

Evidently under polar conditions the formed nitrone–olefin is favorably predisposed to undergo spontaneous intramolecular 1,3-dipolar-cycloaddition. Extensive NMR analysis was carried out to establish both the structure and conformation of the cyclized products.[9]

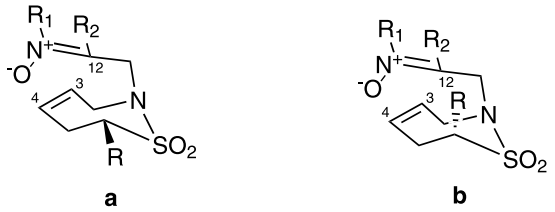


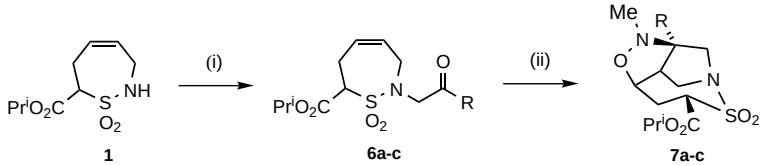
Figure 3. (a) Favored transition state. (b) Disfavored transition state, R = COO^{i}Pr.

Complete ^{1}H and ^{13}C NMR assignment consistent with the structures shown was obtained by 1D and 2D homo- and heteronuclear experiments.

Simple analysis of the intermediate nitrone adducts indicates only one feasible transition state is possible in which the tethered *Z*-nitrone (as shown in **5**; presumably formed with high selectivity) regiospecifically approaches the olefin of the sultam (in its favored chair-like conformation) to gain O–C4 and C12–C3 orbital overlap (Fig. 3). The *Z*-nitrone establishes the stereochemistry at C-12 of the product tricycle while the concerted nature of the cycloaddition defines the stereospecific *cis* addition and thus the orientation of the newly formed chiral centers at C-3 and C-4. Since the tethered-nitrone sultam is an enantiomeric mixture we might expect diastereomers. However, it is clear from the proposed transition state that the isopropyl ester at C-6 favorably adopts a pseudo-equatorial position. The alternative pseudo-axial ester results in a transition state (Fig. 3) that is far too hindered. Thus, the remote C-6 substituent exerts complete asymmetric induction; the enantiomeric starting material reacting via enantiomeric transition states to produce an enantiomeric mixture of products in which three new chiral centers have been established with complete specificity.

The transition state model is in agreement with the structures and conformation inferred from the NMR analysis. Unequivocal proof of the structures proposed was obtained from the X-ray diffraction of crystals of the highly functionalized tricycle **7a** (Fig. 4).[10]

To maximize the chemical diversity that could be introduced into the novel product template three alternative hydroxylamines were investigated (Scheme 3). Reaction of the ethyl ketone **6a** with benzylhydroxylamine (2 equiv.) in the presence of sodium acetate (4 equiv.) and ethanol at room temperature overnight yielded the tricycle **7a** in 67% yield. The bulkier cyclohexylhydroxylamine reacted similarly at 75°C over 24 h to afford **7b** in 47% yield. However, the *tert*-butyl hydroxylamine



Scheme 2. (i) XCH_2COR, K_2CO_3, DMF where (a) X = Br, R = Et, 91%, (b) X = Cl, R = Me, 60%, (c) X = Br, R = Ph, 84%. (ii) MeNHOH·HCl, NaOAc, EtOH.

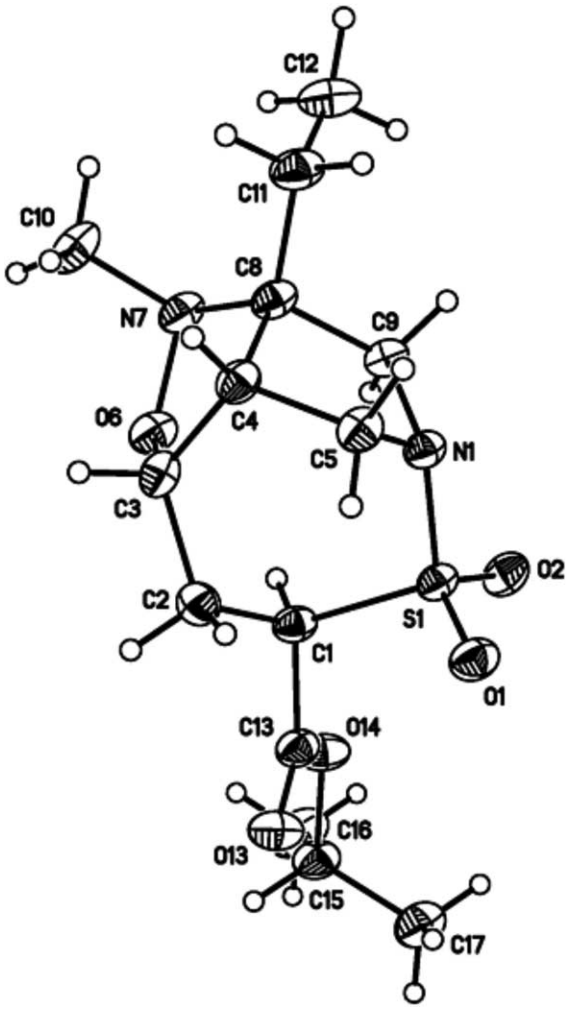
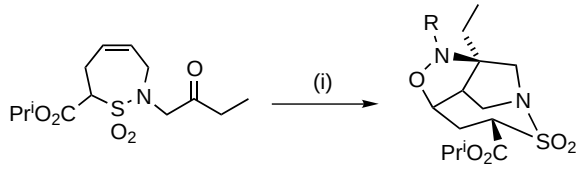


Figure 4. X-Ray crystal conformation of **7a** with C-6 ester in pseudo-equatorial position.



6a **7a-c**

Scheme 3. (i) RNHOH, NaOAc, EtOH where (a) R = Bn, 67%, (b) R = cyclohexyl, 47%, (c) R = Me, 94%.

did not yield any tricyclic product only starting ketone and decomposition products could be recovered. Obviously increased steric encumbrance of both the hydroxylamine and the ketone substituent result in loss of reaction efficiency.

In conclusion we have successfully functionalized the olefin moiety of a sultam template in a exquisitely regio- and stereospecific fashion via an intramolecular nitrone–olefin cycloaddition precisely establishing three chiral centers in a single step. Furthermore, we have highlighted the stability of a rare bridgehead polycyclic framework and indicated its applicability as a combinatorial template.

Experimental procedure

7a: Methylhydroxylamine hydrochloride (46 mg; 0.55 mmol) and sodium acetate (121 mg; 1.48 mmol) were added to a stirred solution of **6a** (112 mg; 0.37 mmol) in ethanol (5 ml). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen. After 24 h LC–MS indicated complete conversion of the starting material to a single product peak. The reaction mixture was concentrated in vacuo and the residue dissolved in chloroform (8 ml) and washed with 2% sodium bicarbonate solution (4 ml). The aqueous layer was extracted with chloroform twice and the organic layers combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate:hexane 3:2–2:1) to yield **7a** (115 mg, 94%) as a white crystalline solid. A sample was recrystallized from ethyl acetate/hexane 2:1).[10]

Acknowledgements

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10. For crystal structure and extensive spectral analysis of **8a** and other compounds reported in this paper, see: Ref. 9.